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Intraindividual and Interindividual Differences in Spontaneous Eye Blinking: Relationships to Working Memory Performance and Frontal EEG Asymmetry

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Abstract

The rate and timing of spontaneous eye blinking (SB) may be used to explore mechanisms of cognitive activity in infancy. In particular, SB rate is believed to reflect some dimensions of dopamine function; therefore, we hypothesized that SB rate would relate to working memory performance and to frontal electroencephalogram (EEG) asymmetry. Forty, 10-mo-old infants completed an A-not-B task while SB and EEG were measured throughout. We found that SB rate varied across phases of the task, variability in SB rate was positively related to working memory performance, and frontal EEG asymmetry was related to individual differences in the rate of SB. Results provide indirect, but convergent support for the hypothesis that SB rate reflects dopamine function early in human development. As such, these results have implications for understanding the tonic and phasic effects of dopamine on cognitive activity early in human development.

Keywords

spontaneous eye blinking; working memory; frontal EEG asymmetry; attention; infancy; dopamine

Introduction

Spontaneous eye blinking (SB) may emerge as a useful tool to help explore mechanisms and development of cognitive function early in human life. SB rate has been used in adult primates as an index of dopaminergic function, and the timing of SB is related to cognitive activity. Evidence that spontaneous eye blinking in primates is regulated at least in part by the central dopamine system (DA) comes from various sources. Notably, experimental manipulations using DA agonists/antagonists in non-human primates (Jutkiewicz & Bergman 2004; Kleven, Koek 1996; Karson, 1983) systematically alter SB rate with agonists increasing the rate of blinking. Also, clinical conditions involving DA function produce predictable changes in SB rate (Parkinsons: Blandini, Nappi, Tassorelli & Martignoni, 2000; Deuschel, & Goddemeier, 1988; schizophrenia: Freed, 1980; Mohr, Sandor, Landis, Fathi &

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Brugger, 2005). Convergent evidence across several species and levels of analysis suggests that some component(s) of central dopamine system regulate SB rate (see review by Bacher and Smotherman, 2004). Although some argue that striatal DA plays a major role (e.g., Colzato, Slagter, van den Wildenberg & Hommel, 2009), the specific mechanisms regulating SB rate within the DA system remain to be clarified.

Numerous studies of adult humans have documented systematic changes in SB rate during a variety of cognitive activities (see Stern, Walwrath & Goldstein, 1984, for review; De Jong & Merckelbach, 1990; Papadelis, Kourtidou-Papadeli, Bamidis & Albani, 2007). For example, activities influencing SB rate include: speaking (von Cramon & Schuri, 1980), reading (Bentivogolo, Bressman, Cassetta, Carretta, Tonali & Albanese, 1997) and cognitive control (Müller, Dreisbach, Brocke, Lesch, Strobel & Goschke, 2007).

Cognitive activities can temporarily alter SB rate. For tasks involving visual attention, blink rate is often reduced during periods of heightened visual engagement (Fukuda, Stern, Brown, & Russo, 2005; Tada, 1978; Oh, Jeong & Jeong, 2012). Some propose that blinks are inhibited to minimize loss of visual information because visual cortical activity is suppressed during blinks (Bristow, Haynes, Sylvester, Frith & Rees, 2005; Volkman, Riggs & Moore, 1980). However, higher cognitive load, whether or not visual attention is involved, may reduce blinking rate (Siegle, Ichikawa & Steinhauer, 2008; Fukuda, 1994). Blinks may also interfere with some aspects of cognitive processing (Thomas & Irwin, 2006) as well as reflect cognitive processing. In addition to cognition, SB rate may be influenced by state (arousal, e.g., De Jong & Merckelbach, 1990) and may be associated with some dimensions of personality (Colzato et al., 2009; Pauls, Wacker & Crost, 2005).

Studies of SB in adults demonstrate that DA participates in the regulation of SB rate and that the rate of SB is sensitive to information processing demands; however, relatively little is known about SB during infancy. The current literature on SB in infants and children is small, but growing. Zametkin, Steven and Pittman (1979) were among the first to describe the low rate of SB in infants (2–3 blinks per min) and to document the developmental increase in SB that plateaus in young adulthood (using a cross sectional design). More recently, others have confirmed this very low rate of SB in infants (Bacher & Smotherman, 2004; Lavezzo, Schellini, Padovani & Hirai, 2008) and employed longitudinal design to examine developmental change in SB (Bacher, 2013; Descroix, Charavel, Witkowski, & Graff, 2015).

As demonstrated with adults, SB rate in infancy can be altered by behavior (feeding, Bacher & Smotherman, 2004a; visual attention, Bacher & Allen, 2009; and social engagement, Bacher, 2013). Clinical work in children also illustrates changes in blinking rate during cognitive activity and group changes in rate associated with certain DA-related clinical conditions (e.g., ADHD, Salman & Liu, 2013; Pivik & Dykmann, 2004; Caplan, Guthrie, & Komo, 1996; fragile x syndrome, Roberts, Symons, Johnson, Hatton & Boccia, 2005). Generally, the pattern of results in studies of infants and children suggests some developmental continuity of behavioral effects and regulatory mechanisms with that of adults.

The present study extends the literature on SB in early human development in two unique ways by investigating SB during a working memory (WM) task and by examining SB in relation to frontal EEG asymmetry (FA). Selecting a WM task was guided by research with infants (Diamond, 1985; Diamond, 1998) and adults that demonstrates dopamine's role in WM (Cools, Gibbs, Miyakawa, Jagust & D'Esposito, 2008; see Cools, 2011 for review). Pursuing FA was based on work that shows or predicts a relationship between DA and frontal EEG asymmetry in infants (Schmidt, Fox, Perez-Edgar & Hamer, 2009) and adults (Wacker, Mueller, Pizzagalli, Hennig & Stemmler, 2013; Allen, Iacono, Depue & Arbisi, 1993). The next sections selectively review these literatures.

Working Memory

A wide range of work supports a role for DA in WM. Studies of adult humans (Cools, 2011; Landau, Lal, O'Neil, Baker, & Jagust, 2008; Aalto, Bruck, Laine, Nagren & Rinne, 2005), clinical populations (Parkinsons in Moustafa, Sherman & Frank, 2008) and other mammals (Romanides, Duffy & Kalivas, 1999; Robbins & Arnsten, 2009) explored the structures and conditions of DA involvement in WM. Cools (2011) describes several models of DA involvement in higher level cognition that includes direct and indirect effects and describes relationships among several structures including striatum, prefrontal cortex and other regions. A recent review by Westbrook and Braver (2016) describes the roles of DA in WM: tonic DA supporting stability of representations in WM, and phasic DA facilitating updating of representations.

In infants, although direct measures of DA were not used, Diamond's work made a significant contribution toward understanding the role of DA in frontal areas that subserve WM tasks (see review Diamond, 2002; Diamond, 1998). This and subsequent work has greatly expanded our understanding of WM in infancy. Notably, WM is apparent in a range of tasks and settings as early as 6–9 mos and the duration of information retention increases substantially from 8 mos and beyond (see review Pelphrey & Reznick, 2003). Although direct measures of DA are still not routinely available in typically developing infants, studies using electroencephalogram (EEG) have revealed that performance on WM task is linked to frontal brain regions (e.g., Bell, 2001; Bell & Fox, 1997). For example, Cuevas and colleagues (Cuevas, Bell, Markovitch & Calkins, 2012) found that task-related EEG power in the medial and lateral regions predicted WM performance at 10 mos. Therefore, we predicted that performance on a WM task would relate to SB rate.

Frontal Asymmetry

The second focus of this investigation was to test for an association between SB rate and frontal EEG asymmetry. Frontal EEG asymmetry (FA) refers to quantitative differences in EEG activity between left and right frontal hemispheres. Davidson's model (1993) asserts that FA indicates brain activities that moderate approach/withdrawal motivational tendencies. Coan and Allen (2004), building on this work, proposed that the mediating functions of FA may be observed during state-related changes in FA and that resting FA may function as a moderator in studies demonstrating individual difference variables. Given DA's role in approach motivation (Depue & Collins, 1999; Berridge, 2007), Allen, Iacono, Depue and Arbisi (1993) hypothesized that DA may, in part, underlie resting frontal EEG. They

tested this hypothesis and found that adults with higher rates of blinking showed greater left frontal activity which is associated with approach-related behaviors (Allen, Kline, Myers, Coan & Dikman, 2014).

More recently, Wacker and colleagues (Wacker, et al., 2013) explored FA as a trait variable and observed an association between FA and DA using both pharmacological manipulation and genetic analysis. They found that trait approach motivation was associated with greater left than right frontal activity, and that FA was related to COMT, a genetic variant related to the modulation of prefrontal DA (Matsumoto, Kanno, Togashi, Ueno, Otani, Mano, & Yoshioka, 2003). The COMT-asymmetry effect was observed in regions including the mid-frontal and lateral frontal areas. Notably, these effects were dependent on the context. Taken together, these studies provide an empirical and theoretical basis for predicting a relationship between DA (as measured by SB) and FA in infants.

Research on FA in infants has generally followed a similar pattern as that with adults. The bulk of studies of infant FA have investigated relations between resting FA and individual differences in temperament and emotional responsiveness. For example, greater left frontal activation is associated with positive affect and easy temperament (Fox, Henderson, Rubin, Calkins & Schmidt, 2001). Further, individual differences in FA show some prediction of later behavior. For example, greater right FA activation during infancy is associated with later behavioral inhibition at 14 and 24 mo (Fox, Calkins, & Bell, 1994; Fox, Henderson, Rubin, Calkins, Schmidt, 2001) and later internalizing behaviors at 24 mos (Smith & Bell, 2010).

Although no studies of infant FA explicitly investigate whether short term changes in FA may be linked to infant cognition, two studies are relevant. Schmidt (2008) examined the short term stability of FA in 9-mo-old infants and found that over 90-s interval, resting EEG could be used to identify infants with a left frontal, a right frontal or a variable pattern of activity. In another report, Schmidt, Fox, Perez-Edgar and Hamer (2009) identified an association between FA and DA showing that resting FA only predicted later temperament for certain DRD4 receptor types. Children with the long allele and more left frontal activation showed a different behavioral pattern at 4 years than children who exhibited right frontal FA and did not possess the long allele. Although pursuing different goals, Schmidt's work demonstrates that examining short term features of FA is feasible and useful, and that FA in infancy is related to the DA system.

The present investigation examined SB during a WM task in typically developing 10-month-old infants. Infant WM ability increases dramatically in the first year with basic competence in tracking object locations by 9 mos (Cuevas et al., 2012; Cuevas & Bell, 2010; Diamond, 1985; Kibbe & Leslie, 2013;). We used a looking version of the A-not-B task which has been widely used to assess WM in infants (Bell & Adams, 1999; Cuevas et al., 2012) but also requires effortful attention and inhibitory control (Bell, 2012; Bell & Adams, 1999; Diamond, et al. 1997).

While infants were performing the A-not-B task, SB and EEG were measured continuously. It is established that SB rate exhibits both task-related effects and wide individual

differences that have been linked to other behavioral and physiological variables. The following hypotheses incorporated both state and trait measures of SB. First, SB will be associated with WM. If tonic SB rate reflects central DA function and DA is related to WM, then differences in SB rate may be observed for differential performance on the WM task. However, the association between cognitive performance and DA may be non-linear (inverted u-shape) with better performance at intermediate levels of DA (Cools & D'Esposito, 2011). Also, some cognitive tasks elicit phasic changes in SB rate. Therefore, we expected to observe systematic changes in SB across the task that would reflect performance on the task. Also, we expected that SB rate will be lower under greater conditions of cognitive load (Siegle, Ichikawa & Steinhauer, 2002). Greater cognitive load is expected during the objecting-hiding phase of a WM task.

Second, we hypothesized that SB will be associated with FA; infants with higher rates of blinking will exhibit greater left-frontal activation which is associated with more approach-related behaviors. Due to FA sensitivity to context, we also anticipated FA differences across phases of the WM task.

We believe this to be the first analysis of SB during a WM task in infants as well as the first examination of a link between SB and FA in infants. Our results will provide unique information about the role of dopamine function in WM and frontal EEG asymmetry in infancy. Further, the present investigation expands our understanding of FA by examining it in the context of a cognitive task.

Investigations of spontaneous eye blinking may offer new insights into behavioral and neurological development in human infants because of its relationship to dopamine system function and information processing. Although it is clear that direct testing of the SB-DA relationship is needed, initial empirical and theoretical support justifies the present, cautious use of SB as a marker for DA. Additionally, understanding the mechanisms and development of executive function (e.g., WM, attention regulation) is important for both educational and clinical applications (Blair & Razza, 2007; Miyake, Friedman, Emerson, Witzki, Howerter & Wager, 2000; Moffitt, Arseneault, Belsky, Dickson, Hancox, Harrington, Houts, Poulton, Roberts, Ross, Sears, Thomson & Caspi, 2011).

Method

Participants

Participants in our study included infants and their mothers from one cohort of a longitudinal study of individual differences in cognitive and socio-emotional development. Mothers with 5-month-old infants were recruited through a commercial mailing list of new parents. All 105 infants were healthy with no prenatal, birth, or postnatal complications. These analyses focused on the data from a subsample of mothers and infants who visited the lab when children were 10 mos old. Infants were selected for inclusion in our subsample study to achieve the following: equal numbers of boys and girls, equal numbers of high and low performers and performance on the A-not-B task that included correct and incorrect trials, and trials lasted at least 3 min. The final sample was $n = 40$. For the overall sample, mothers reported that their children were primarily Caucasian (91%) with 8% multiracial and 1%

African American or other. Two percent of mothers did not complete high school, 30% had earned high school or technical degrees, and 68% were college graduates. The demographics of the sample reflect those of the relatively homogeneous population surrounding the small college town in rural Appalachia where the study was conducted. The subsample of infants selected for the analyses in this report were similar in demographics to the larger cohort.

To better examine factors relating to differences in performance on the A-not-B task, 20 high performing and 20 low performing infants were selected for the subsample. Selection began with the highest and lowest performing infants, selecting equal numbers of boys and girls in each group, and selecting participants with both successful and failed trials.

Procedures

Infants and their mothers visited the research lab on or within two weeks after their 10-month birthdays. The EEG cap was placed on the infant's head and then the child participated in the A-not-B task, along with other tasks reported elsewhere (blinded for review). At the end of the assessment, mothers were paid for participating.

A-not-B task—The testing apparatus was a table measuring 90 cm (L) x 60 cm (W) x 75 cm (H) and the hiding sites were bright orange and blue plastic tubs that measured 17 cm in diameter and 11 cm deep. The infant sat on the parent's lap 1.1 m from the edge of the testing table as the experimenter manipulated a toy and hid it under one of the two (17.5 cm on either side of midline) plastic tubs. The infant searched for a hidden toy by making an eye movement to one of two possible hiding locations. Much like the reaching version of the infant WM task (the classic A-not-B task), the looking version required the infant to constantly update memory of where the toy was hidden through a series of displacements and to inhibit looking back toward a previously rewarded hiding place (Bell & Adams, 1999; Bell, 2001, 2012).

After the toy was hidden, the infant's gaze to the hiding site was broken and brought to midline by the experimenter calling the infant's name and asking, "Where's the toy?" The direction of the infant's first eye movement after being brought to midline was scored as either correct or incorrect. A video camera was placed behind and above the experimenter's head and focused so as to maintain a close-up view of the infant's face. Because the infants were not allowed to manipulate the toys, the visual experience they received from the moving, mechanical toy and the smiles and praise they received ("Good job! You found it!") from the experimenter after an eye movement to the correct tub had to provide the impetus to continue to search for the toy. For an eye movement to the incorrect tub, the infants received a sigh and sad vocalizations from the experimenter ("Oh, no. It's not there.").

The pattern of toy placement was determined by the infant's performance, with initial side of hiding randomized among infants (Bell & Adams, 1999). Two consecutive successful eye movements toward the same side (for example, toward the infant's right) resulted in a reversal hiding, with the toy being hidden under the tub on the opposite side (toward the infant's left; i.e., Right-Right-Left). All infants received reversal trials. Regardless of whether or not the infant was successful on the reversal trial, new "same-side" trials commenced at the reversal site and continued until two consecutive successful eye

movements were executed, initiating another reversal (i.e., L-L-R). Thus, flawless performance by an infant would result in this pattern of trials: R-R-L-L-L-R-etc. In reality, most infants were not flawless in performance and some needed multiple same-side trials in order to achieve two consecutive successful eye movements prior to reversal trials (e.g., L-L-L-L-L-R-R-R-R-L-etc.). Assessment ceased when the infant made an eye movement toward the incorrect side in two reversal trials.

An event marker was used in conjunction with the EEG recording so that it was possible to mark the portions of the neurophysiological record associated with the specific processing phase of each trial. Thus, the “Display” (*attention*) processing phase was the time period when the experimenter manipulated the toy to capture the infant’s interest and then hid it under one of the two tubs. During “Hide & delay” (*WM and inhibitory control*), the infant’s gaze to the hiding site was broken and brought to the experimenter’s face at midline by the experimenter calling the infant’s name and asking, “Where’s the toy?” This component of the task ended with the infant’s first eye movement. “Reveal & reward” (*emotional feedback to infant*) consisted of the experimenter praising the infant for a correct eye movement (or sighing in the event of an incorrect one) and revealing the toy from the tub for the infant to see (Figure 1; see also Bell, 2002; Cuevas, Raj & Bell, 2012). The experimenter talked to the infant during each of the three processing stages. The artifact-free EEG data from all trials (correct and incorrect) were used in these analyses.

Each trial was composed of three phases: Display, Hide & Delay, and Reveal & Reward phase. Means ($\pm$ SD) for each phase were: Display ($M=8.75 \pm 1.56$ s), Hide ($M=7.34 \pm 1.45$ s) and Reveal ($M=7.33 \pm 1.68$ s). One-way ANOVA followed by post hoc tests indicated that the Display phase was longer in duration than the Hide and the Reveal phases, $F(2,78)=11.7$, $p<.001$ (paired t-tests of Display to Hide and Reveal phases were $p<.001$).

The primary performance measurement on the A-not-B task was proportion correct. Proportion correct calculated by the number of trials with a correct response divided by the total number of trials presented (Cuevas et al., 2012). The average proportion correct for the 20 low performing infants was $M=.40 \pm .11$ (.20 to .54 range) and 20 high performing infants was $M=.80 \pm .06$ (.70 to .92 range; see Table 1).

Spontaneous eye blinking—Trained research assistants reviewed video tapes of infants performing the A- not- B task in order to measure the rate of spontaneous eye blinking (SB) during the task. The camera was kept on the infant’s face while the experimenter conducted the task. If the infant’s face moved out of view, that period of time was excluded from the blink rate calculation. Tapes were reviewed initially with no sound.

Trained research assistants reviewed the video tapes in slow motion tool as well as frame by frame to identify valid SB and the time at which each SB occurred. For an eye closure to be counted as a spontaneous eye blink, the lids must close symmetrically for 250–400ms. Complete closure of the lids is not required (Himebaugh, Begley, Bradley & Wilkinson, 2009). Eye closures due to yawns, sneezes, startles, coughs, grimaces, fussiness or hand movements toward the face or mouth, were not included in the analysis. Asymmetrical and slow eye closures (>450 ms) were not included in the analysis as well (Bacher & Allen,

2009). Difficult segments were coded by two assistants. Inter-rater reliability estimates for these data were above 85% using a percent agreement measure (procedure also reported in Bacher & Allen, 2009). At least 3 min of continuous recording is recommended for reliable estimates of rate of blinking (Zaman & Doughy, 1997).

A separate pass through the video recordings was used to mark the boundaries of the phases of each trial of the A-not-B task. The start of the Display phase began with the experimenter's invitation to look at the toy or the appearance of the toy (whichever was first). The start of the Hide & delay phase began with the toy was no longer visible (when the bucket fully rested on the table). The start of the Reveal & reward phase began when the edge of the bucket lifted off the table. No breaks occurred between phases.

After both the blink coding and the phase coding processes were completed, the SB information was added to the phase information so that the timing of the blinks could be associated with the phase in which it occurred.

Table 1 presents descriptive data for infant observations. Data include: duration of session, number of trials completed, overall blinking rate, WM performance data, and tests of sex differences for primary variables. Blinking rate appeared to be stable during the observation: the number of blinks in the first half of the session ($M=7.70 \pm 4.9$) did not differ from that of the second half ($M=8.88 \pm 5.3$), $t(39)=1.67$, $p=.10$, yet the segment lengths analyzed were often shorter than the recommended 3 min observation (Zaman & Doughy, 1997).

Independent t-tests showed no effects of sex for overall SB rate, WM performance, or FA measures for F8-F7 (Display, Hide or Reveal). However, sex differences in FA were observed at F4-F3 (males then females, Hide: $M=-.1028 \pm .24$, $M=-.1059 \pm .34$, $t(39)=5.06$, $p=.03$; Reveal: $M=-.083 \pm .26$, $M=-.131 \pm .32$, $t(39)=5.3$, $p=.027$), but region F4-F3 was not implicated in any of the other results of this work.

EEG recording and asymmetry calculations—Baseline EEG recordings were collected from 16 left and right scalp sites (frontal pole (Fp1, Fp2); medial frontal (F3, F4); lateral frontal (F7, F8); central (C3, C4); temporal (T7, T8); parietal (P3, P4, P7, P8); and occipital (O1, O2) referenced to Cz during recoding). A small amount of abrasive gel was placed into each recording site and the scalp gently rubbed. Next, conductive gel was placed in each site and the scalp gently rubbed. Electrode impedances were measured and accepted if they were below 10K ohms. The electrical activity from each lead was amplified using separate James Long Company Bioamps (James Long Company, Caroga Lake, NY). During data collection, the high pass filter was a single pole RC filter with a 0.1 Hz cut-off (3 dB or half-power point) and 6 dB per octave roll-off. The low pass filter was a two-pole Butterworth type with a 100 Hz cut-off (3 dB or half-power point) and 12 dB octave roll-off.

Activity for each lead was displayed on the monitor of the acquisition computer. The EEG signal was digitized on-line at 512 samples per second for each channel so that the data were not affected by aliasing. The acquisition software was Snapshot-Snapstream (HEM Data Corp., Southfield, MI). The raw data were stored for later analyses. Prior to the recording of each subject a 10 Hz, 50 uV peak-to-peak sine wave was input through each amplifier. This calibration signal was digitized for 30 seconds and stored for subsequent analysis.

Spectral analysis of the calibration signal and computation of power at the 9 to 11 Hz frequency band was accomplished. The power figures were used to calibrate the power derived from the subsequent spectral analysis of the EEG. Infant EEG data were examined and analyzed using EEG Analysis System software developed by James Long Company (Caroga Lake, NY). First, the data were re-referenced via software to an average reference configuration. The average reference EEG data were artifact scored for eye movements and gross motor artifact. These artifacts scored epochs were eliminated from all subsequent analyses. The EEG data were then analyzed with a discrete Fourier transform (DFT) using a Hanning window of 1-second width and 50% overlap. Power was computed for the 6 to 9 Hz frequency band. This particular frequency band is thought to approximate the alpha band in adults and has been used in previous studies of infant frontal asymmetry (e.g., Bell & Fox, 1994; Buss, Malmstadt, Dolski, Kalin, Goldsmith, & Davidson, 2003; Diaz & Bell, 2012; Fox, Bell, & Jones, 1992; Smith & Bell, 2010). For the current study, EEG power was expressed as mean square microvolts and the data transformed using the natural log (ln) to normalize the distribution.

Frontal EEG asymmetry values were computed according to convention by subtracting ln power at left frontal from ln power at right frontal for the electrode pairs F2-F1, F4-F3 and F8-F7 (Coan & Allen, 2004; Goldstein, Shankman, Kujawa, Orpey-Newman, Olino, & Klein, 2016). In the EEG literature, brain activation is indicated by lower EEG power values in the alpha frequency band (Lindsley, 1936). Thus, a negative asymmetry score reflects greater right frontal activation, whereas a positive asymmetry score reflects greater left frontal activation.

Results

Statistical analyses

The first set of analyses focused on the hypothesis that SB would be associated with WM performance. Tests of state and trait aspects of SB were tested. A second set of analyses focused on the hypothesis that SB would be associated with FA. ANOVA was used to examine whether individual differences in SB rate related to FA during the WM task. Correlations were reported but have limited utility due to potential for non-linear relationships to be present in this data.

For one analysis, the rate of blinking was used to divide infants into three groups (see Table 1). If SB rate reflects stable individual differences in some aspects of neurological function, this division allows us to test for non-linear relationships as identified in adult samples for some cognitive tasks.

Tests of Hypothesis 1: SB is related to WM performance

A two-way mixed ANOVA tested for differences in SB rate by WM performance (High, Low) and phase (Display, Hide, Reveal). SB rate varied across phase, $F(2,74)=3.78$, $p=.036$ (with Greenhouse-Geisser correction). Repeated contrasts indicated a significant quadratic relationship for phase, $F(1,38)=4.90$, $p=.033$. No relationship between WM performance and

SB was found, $F(1,38)=.90$, $p=.35$, nor was an interaction observed, $F(2,76)=.013$, $p=.99$ (see Figure 2). The effect size for phase, as estimated by partial η^2 , was .09.

To further examine individual differences in SB rate, we tested whether the amount of within-subject variability in SB *across phases* (Display, Hide, Reveal) was related to WM performance. The mean of the absolute differences in SB across phases (2.3 blinks per min) was used to create two groups. Independent t-test showed that infants whose SB rate exhibited greater change across the three phases performed better on the task than infants whose blinking rate did not change as much, $t(38)=-2.19$, $p=.035$ (above mean proportion correct $M=.70 \pm .16$, below mean $M=.54 \pm .23$).

The simple bivariate correlation between SB rate and WM showed no relationship, $r = -.70$, $p=.67$.

Tests of Hypothesis 2: SB is related to FA

A 2-way mixed ANOVA was used to test for differences in FA (separately for each frontal electrode pair: F2-F1, F4-F3, and F8-F7) by individual differences in blinking rate (High, Medium, Low blinkers) and within subjects by phase of the task (Display, Hide, Reveal). This analysis permitted testing whether individual differences in SB may relate to changes in FA over time. An interaction of blinking rate group and phase was observed in the asymmetry measure for the F8-F7 region (Figure 3), $F(2,74)=2.6$, $p=.045$. The effect size for this interaction was, as estimated by partial η^2 , was .12. All other tests results were $p > .06$ (range $p=.06$ to $p=.93$); no effects were observed for regions F2-F1 or F4-F3.

A one-way ANOVA used to further explore the differences in asymmetry during the Display phase revealed a main effect for blink rate group, $F(2,37)=3.4$, $p=.037$, but post hoc tests indicated no significant differences, ($p=.055$ and $p=.97$). Also, asymmetry values for each blink rate group during the Display phase were compared to a test value of 0 (indicating no strong asymmetry). No difference from 0 was observed for low blinkers, $t(12)=1.34$, $p=.21$ or medium blinkers, $t(13)=-1.47$, $p=.17$. However, asymmetry values for high blinkers were significantly higher than 0, $t(12)=2.33$, $p=.038$, indicating left frontal activation.

Simple bivariate correlations showed no relations between SB rate (and SB rate differences across phases) and any of the FA measures (3 locations and 3 phases), r ranged from $-.38$ to $.27$, p ranged from $.06$ to $.91$.

Discussion

Theoretical and empirical work with infants and adults on spontaneous eye blinking as an indicator of dopamine function as well as work on the role of dopamine in WM and FA provided a foundation for our two-fold investigation. First, we examined relationships between SB rate and performance on a WM task. Second, we tested for relationships between SB rate and FA. We used a looking version of the A-not-B task to investigate these relationships in typically developing 10-month-old infants. Both state (task-related) and trait (individual differences) in SB rate were tested in the analyses. After addressing the hypotheses, limitations and conclusions are offered.

SB and WM Performance

SB rate was compared across the phases of the WM task (Display, Hide, Reveal), and SB rate was examined with respect to overall performance on the WM task. Infants' SB rate varied across phases of the task as predicted. Task-related modulation of SB rate has been observed in numerous studies of adults (Siegle, Ichikawa, & Steinhauer, 2008; Fukuda, Stern, Brown, & Russo, 2005; Tada, 1978; Oh, Jeong & Jeong, 2012), children (Caplan, Guthrie & Komo, 1996; Jacobson, Hommer, Hong, Gasellanos, Frazier, Geidd & Rapport, 1996; Pivik & Dykman, 2003; Roberts, Symons, Johnson, Hatton & Borccia, 2005) and infants (Bacher, 2013; Bacher & Allen, 2009; Bacher & Smotherman, 2004a). Changes in SB rate were expected to occur as task demands changed across phases of the WM task.

During the WM task, SB rate fluctuated within trials and exhibited relatively lower SB rate during the Reveal phase than the Hide phase. Although performance on the A-not-B task did not relate to individual differences in the overall rate of SB (to be discussed later), the analysis of *within-subject change in SB* did relate to task performance. We found that greater variability in SB rate during the WM task was related to better performance on the task. This result demonstrating fluctuations in SB rate across phases of the trials represents a unique example of systematic modulation of SB during a cognitive task early in human development.

This modulation of SB rate across task phases could be interpreted in different ways. In terms of WM performance, the modulation of SB rate might reflect the engagement of cognitive resources during the Hide phase that are released or not required during the Reveal phase. Work with adults suggests that DA regulates the maintenance and updating of representations in WM (see review by Westbrook & Braver, 2016). Here, the relative drop in SB from Hide to Reveal could reflect that DA had been transiently elevated as infants were prompted to update and maintain their mental representations of the object's location (during Hide). A study of 8-mo-olds observed a similar pattern in SB rates during a task that required infants to learn a new rule (Werchan, Collins, Frank & Amso, 2015). In that study, infants' SB rates had increased selectively on trials following rule acquisition compared to trials that did not require the new rule. Notably, these two observations of infants appear to be inconsistent with a pattern of SB observed in adults. During higher cognitive load, Siegle, Ichikawa and Steinhauer (2008) observed that SB rate was reduced. In the present WM study, the Hide phase was expected to have the greater load, yet SB rate was relatively higher.

A second, more parsimonious, interpretation is that infants whose attention to the toy is elicited more strongly or consistently (showing greater change in SB rate across phases) performed better on the task due to better tracking of the toy location or task engagement. This interpretation is consistent with work demonstrating that SB rate tends to be lower during tasks that require visual attention (Bacher & Allen, 2009; Fukuda et al., 2005; Oh, Jeong & Jeong, 2012). Greater elicitation of visual attention was expected during the phases when the experimenter was manipulating the toys (Display and Reveal phases) but not when the toy was hidden.

Another interpretation of the SB rate modulation during each trial may be described in terms of motivation or incentive salience (Berridge, 2007). Shultz, Klin and Jones (2011) argued that a relative reduction of blinks could be used to infer salience of viewed events. Although it is difficult to disentangle attention and salience because attention is often elicited to salient objects and events, the greater modulation of SB with better WM performance could suggest sensitivity to the reward potential of the toy. The changes in affective intensity across the phases could promote attentional engagement, further enhancing the salience of the objects presented. These three interpretations of the modulation of SB rate are not necessarily incompatible; SB rate may not offer the precision to discriminate among closely linked functions. The larger implication of the link between fluctuations in SB and WM performance is that, in some cases, SB variability may be a useful index of DA engagement in cognitive tasks.

For the analysis of individual differences in SB rate in relation to WM performance, high and low performers on the A-not-B task did not differ in rate of blinking. Methodological challenges may have prevented observing the predicted relationship. Cools and D'Esposito (2011) present evidence that the DA-WM relationship in adults is non-linear and reflects both phasic and tonic aspects of DA function. Therefore, one must know the baseline (tonic) level of DA and understand the effect of the task on DA (phasic change) in order to observe the DA-performance relationship. However, in this particular design used with infants, a true baseline measurement of blinking was not obtained. It is prohibitively difficult to elicit several minutes of quiet looking from infants of this age, and so the blinking rate groups were based on blinking rate throughout the observation. Alternatively, it is possible that the adult pattern is not present in infants or that the low rate of SB in infants restricts too greatly the range of possible SB rates for a non-linear pattern to manifest.

SB and FA—The second focus of this investigation was to test whether individual differences in rate of blinking were related to FA. Our results indicated that FA at the F8-F7 electrode sites emerged over a period of seconds during one phase of the task. More specifically, FA measures diverged by blinking rate groups during the Display phase. During the Display phase, infants with high blinking rates had elevated left frontal activation. Infants with low blinking rates were not distinguishable from the high blinking infants or the intermediate blinking infants.

This finding is discussed in terms of time scale, brain region, task phase and the non-linear pattern of FA for blinking groups. With respect to time scale, our finding shows that FA varied systematically on a time scale about 25 sec (duration of trials) with stable asymmetry observed between 6–12 sec (range of Display phase duration). Although FA work in infants has historically focused on identifying stable individual differences in resting FA that relate to behavioral traits (Saby & Marshall, 2012), several recent studies have emphasized the state-dependent features of FA (Wacker et al., 2013; Boksem, Kostermans, Tops & De Cremer, 2012; Papousek & Schuster, 2004; Goodman, Reitschel, Costanzo & Hatfield, 2013; Diaz, & Bell, 2012). Our finding indicates that short-term FA changes induced by task demands may relate to different cognitive activities, and that one of the activities (during Display) reflects individual differences in infants that underlie SB rate.

The EEG asymmetry was observed at the lateral frontal, F8-F7 scalp locations, an area that has been associated with attention in infancy (Grossman, 2013). Notably, Cuevas and colleagues (Cuevas et al., 2012) found that EEG power at frontal scalp areas F8-F7 and F4-F3 predicted WM performance at 10 mos. The subset of infants studied here partially replicates the finding with the larger group of 306 infants reported by Cuevas and colleagues. In adults, Wacker et al. (2013) observed a pattern similar to our results: asymmetry in F8-F7 was related to individual differences in DA and was context-dependent. Other work also shows that DA effects are highly dependent on task demands (Cools, Barker, Sahakian & Robbins, 2001; Aarts, van Holstein, & Cools 2011).

More broadly, the region F8-7 in adults is part of the dorsal attention network which is associated with externally directed attention (Corbetta & Shulman, 2002; Ptak & Schnider, 2010). Notably, Gao and colleagues report evidence of developmental continuity of brain networks starting about 1 year (Gao, Zhu, Giovanello, Smith, Shen, Gilmore & Lin, 2009). Therefore, it is possible that our results reflect the early expression of the dorsal attention network during the Display phase and tonic DA differences influence that expression.

The observation of the SB-FA relationship during the Display phase of the task invites interpretations in terms of attention and motivational salience. The unique features of the Display phase in comparison to the other phases are its attention-eliciting features and positive emotional tone (see Methods for details). Thus, the context in which the asymmetry was observed (Display phase) was characterized by the experimenter's actions and emotional tone designed to elicit high levels of visual attention and potentially invite approach-related behaviors. Our observation of short-term FA may parallel work showing that left frontal activation in resting EEG is linked to stable approach-related tendencies in infants and adults (see review by Saby & Marshall, 2012; Davidson, 1993; Allen, Kline, Myers, Coan & Dikman, 2003). If the typical interpretation of resting FA applies also to short term emergence of FA, one might suggest that approach motivation in the high blinking infants was elicited during the Display phase (Depue & Collins, 1999; Allen, et al., 2003; Davidson, 1992). However, because transient FA patterns are less well investigated, it is unclear whether the approach/withdrawal distinction is appropriate with short term, task-induced emergence of FA.

Although high blinking infants showed significant left frontal activation and the other groups did not, the infants with an intermediate rate of SB had a trend toward right activation. Non-linear patterns between DA levels and behavior have been documented in other studies and were predicted here. For example, Cools and D'Esposito (2001) have observed an inverted u-shape function between DA and some types of cognitive performance (including WM), with intermediate levels of DA associated with better performance. In the present analysis, high blinkers showed left frontal activation, but the other groups did not show strong left or right activation. Further work exploring these individual differences in SB using larger samples is needed.

Results suggest that individual differences in tonic DA (as measured by SB rate over minutes) were associated with the emergence of transient expressions of FA, but phasic changes in SB were not associated with emergence of FA. When SB rate increased at the

Hide phase, FA diminished. This pattern suggests that, for this observation, DA was functioning as a modulator rather than a mediator (Allen, Kline, Myers, Coan & Dikman, 2014).

Further, the FA was not apparent in the Reveal phase where the emotional intensity of the experimenter was greatest. It is noteworthy that emotional valence varied between trials depending on whether the infant looked at the correct toy location or not. Further work with a larger sample could examine FA separately for successful and unsuccessful trials in order to assess the potential contribution of emotional valence to the expression of FA.

Limitations—Three limitations particular to this investigation are noted, and two more general limitations are presented. First, the analysis of blinking rate was not based on a quiet baseline period as is ideal. Asking infants of this age to sit quietly with little stimulation for several minutes is not feasible. Therefore, we used the average SB rate for the whole session to form groups by SB rate. Our analyses indicated that while SB rate was modulated across the task phases, individual differences in blinking rate were much larger than the transient increase in rate at the Hide phase. Therefore, the assignment to blinking group was not likely to be influenced by transient changes in rate. However, this limitation makes comparison of blinking rate to other studies of infants more difficult because no true baseline was available.

Second, inferences about visual attention were made when interpreting the results, but direct measures of direction of infant gaze were not used. Future researchers should include measures of the direction of gaze and SB during cognitive tasks to confirm the extent to which transient increases in visual attention are temporally associated with decreases in SB rate in late infancy.

Third, effects of the experimenter's emotional tone were confounded with performance on the task. During each Reveal phase, the experimenter's emotional response was related to whether the infant was successful on the trial. While this is an important dimension of this particular task, for the present analysis of FA it meant that we could not separate the effects of cognition (task performance) and affect (emotional tone of experimenter) on FA. A larger sample of infants would permit the reliable analysis of FA during successful and unsuccessful trials and test whether carryover effects were present from the Reveal to the Display phase. Importantly, post-hoc analysis of the SB rate for successful versus unsuccessful trials yielded no difference. Affective tone only varied only between successful and unsuccessful trials. Therefore, affective tone of the experimenter did not appear to affect SB rates.

A more general limitation of work with SB rate in infants is that the short term stability of SB over hours and days has not yet been established. A modest amount of developmental stability has been noted between 4 and 12 mos (Bacher & Allen, 2009), but no studies of blinking stability in infants are available that focus on short time frames such as hour to hour, day to day, or week to week.

Finally, direct measures of DA in healthy human infants are not yet available. Therefore, until such measures can be made, the assertion that SB rate reflects DA in infants is based on

converging evidence obtained from a wide range of behavioral, clinical and pharmacological studies. Future work must test this assertion directly in infants and children and must identify the specific aspects of the DA system that relate to SB rate. Future work on SB should (a) confirm the nature of the relationship between SB and DA using more direct measures, (b) describe the stability of SB rate over several time scales, (c) identify developmental consequences of individual differences in SB rate, if any, (d) explore the relationships of cognitive activity and effect on SB rate, and (e) replicate and explore the mechanisms and implications of the relationship between SB and FA.

Conclusions—Most basically, if SB rate in infants reflects some aspects of DA function, then these results help identify dopamine-regulated aspects of information processing early in human development. Several more specific conclusions and speculations may be drawn from these results.

First, results provide indirect evidence of DA involvement in WM in infants toward the end of the first year. Better WM performance was observed in infants who expressed greater variability in SB rate, but overall SB rate was not related to WM. This may indicate that phasic changes in DA are more indicative of WM performance than tonic levels at this time in development. More specifically, the variability in rate may reflect transient changes in DA when infants are creating or maintaining representations of hidden objects (Werchan, Collins, Frank & Amso, 2015; Westbrook & Braver, 2016).

Also, this observation of SB modulation relating to WM performance prompts a predication that as development proceeds, greater fluctuation of SB rate could reflect wider modulation of central DA and thus relate to better performance during maturation. Also, the observation of gradually increasing SB rates in development could signal greater tonic DA range or capacity. Methodologically, variability in SB rate, as well as baseline rate, may be a useful index for the exploration of cognitive ability.

Second, the short term, we found that task-related changes in FA during cognitive tasks can reveal individual differences among infants. Individual differences in SB rate produced different FA patterns across phases of the WM task. This could mean that individual differences in tonic DA levels were the basis for these FA patterns and, if so, these differences could underlie the relationships between cognition, motivation and personality that have been observed (Aarts, van Holstein & Cools, 2011; Wacker, Chavanon, & Stemmler, 2006) and are of increasing interest to scientists (Westbrook & Braver, 2016). For example, functions of certain aspects of the central DA system may be the underlying process that underlies some associations among these higher order constructs.

In closing, WM and attention regulation are foundational components of executive function that have significant implications for later cognitive outcomes (Blair & Razza, 2007). Cuevas and Bell (2014) showed that individual differences in attention at 5 mos were related to EF in early childhood. Moreover, executive functions are important in many facets of human life including physical health, mental health, and even job success (see review by Diamond, 2013). Therefore, understanding the mechanisms and development of these abilities is important to both basic and applied research in human development.

Moreover, the exploration of SB in infants continues to yield interesting and useful relationships to other behavioral and neurophysiological systems, and the pattern of results to-date generally shows continuity with that of adults. Although many questions remain, the further pursuit of the correlates and mechanisms of SB may yield more targeted hypotheses in future studies of the development of cognition and motivation.

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Figure 1.

Trials were composed of 3 phases: Display, Hide & Delay, Reveal & Reward. Multiple trials were given for each infant.

Figure 2.

Mean (SD) spontaneous eye blinking rate (SB/min) by phase (Display, Hide, Reveal).

Asterisk denotes differences between pairs of means.

Figure 3. Mean frontal EEG asymmetry for region F8-F7 by phase (Display, Hide, Reveal) and individual differences in SB rate (Low, Medium, High blinking rate).

Table 1

Descriptive data for sessions and infant characteristics. Top panel shows session characteristics, WM performance groups and blinking rate groups. The lower panel shows infant blink rate, WM performance, and FA data by infant sex.

	Mean $\pm$ SD	N	Min - Max
Duration of session (sec)	279.1 $\pm$ 62.4	40	179 – 430
Number of trials completed	12.0 $\pm$ 2.7	40	8 – 20
Duration of each phase (sec)			
Display	8.75 $\pm$ 1.56	40	6.08 – 12.7
Hide	7.34 $\pm$ 1.45	40	4.54 – 11.3
Reveal	7.33 $\pm$ 1.68	40	4.60 – 11.3
Blink rate for session (SB/min)	3.66 $\pm$ 1.82	40	.84 – 9.0
High blink rate	7.5 $\pm$ 1.6	13	
Medium blink rate	3.1 $\pm$.39	14	
Low blink rate	2.1 $\pm$.55	13	
WM performance (proportion correct)	.59 $\pm$.22	40	.20 – .92
High performers	.80 $\pm$.06	20	.70 – .92
Low performers	.40 $\pm$.11	20	.20 – .54

	Group M $\pm$ SD	
	Girls (n=20)	Boys (n=20)
SB rate (SB/min)*	3.80 $\pm$ 1.89	3.45 $\pm$ 1.77
WM performance* (proportion correct)	.62 $\pm$.19	.58 $\pm$.25
Frontal EEG asymmetry*		
F8-7 Display	.0254 $\pm$.34	.0338 $\pm$.27
F8-7 Hide	.0315 $\pm$.33	-.0140 $\pm$.26
F8-7 Reveal	.0553 $\pm$.31	-.0142 $\pm$.24

Note. No sex differences were observed, $p > .05$.